Diurnal profile of interstitial glucose following dexamethasone prophylaxis for chemotherapy treatment of gynaecological cancer

DR MARCUS J LYALL (Orcid ID : 0000-0002-2952-2676)

Article type : Research Article

Title: Diabetic Medicine

Created by: Maria Hale

Email proofs to: mlyall@staffmail.ed.ac.uk

Copyright: Diabetes UK

Article no.: DME-2018-00049

Article type: Research Article

Short title/*Authors running head*: *Glucose profiling during dexamethasone prophylaxis in chemotherapy • M. J. Lyall et al.*

Research: Care Delivery

Diurnal profile of interstitial glucose following dexamethasone prophylaxis for chemotherapy treatment of gynaecological cancer

M. J. Lyall[1], I. Thethy[2], L. Steven[4], M. MacKean[5], F. Nussey[5], M. Sakala[5], T. Rye[5], M. W. J. Strachan[6] and A. R. Dover[3]

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dme.13770

[1]University/British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, [2]Acute Medical Unit and [3]Edinburgh Centre for Endocrinology and Diabetes, Royal Infirmary of Edinburgh, and [4]Wellcome Trust Clinical Research Facility, [5]Edinburgh Cancer Centre and [6]Edinburgh Centre for Endocrinology and Diabetes, Metabolic Unit, Western General Hospital, Edinburgh, UK

Correspondence to: Marcus J. Lyall. E-mail: mlyall@staffmail.ed.ac.uk

What's new?

- Hyperglycaemia during chemotherapy treatment is associated with negative health outcomes.
- The incidence, severity and diurnal profile of glucose dysregulation during chemotherapy are unclear, limiting development of screening and treatment protocols.
- Utilizing continuous glucose monitoring, these data demonstrate that elevated glucose levels affect nearly all women treated with a standard carboplatin/paclitaxel/dexamethasone chemotherapeutic regimen for gynaecological cancer.
- The diurnal profile is described with peak glucose windows for opportunistic monitoring.
- HbA_{1c} was independently associated with the severity and duration of glucose excursions.

Abstract

Aims Hyperglycaemia, a side-effect of acute glucocorticoid exposure, is associated with poor outcome in those undergoing chemotherapy. The incidence, risk factors and diurnal profile of glucocorticoid-induced glucose dysregulation in the context of chemotherapy treatment remain incompletely understood.

Methods Blinded continuous interstitial glucose monitoring was performed on 16 women without diabetes for 24 h prior to and 5 days following carboplatin/paclitaxel chemotherapy combined with dexamethasone treatment for gynaecological cancer. At the end of the treatment period, glucose data were analysed and integrated with baseline metabolic and anthropomorphic variables.

Results Some 15/16 (94%) women exhibited elevated glucose levels (> 11.1 mmol/l). Peak glucose levels were highest on the day of treatment (median 14.45 mmol/l, range 10.2–22.2 mmol/l) and total time spent with an elevated interstitial glucose level was highly variable (median 3.6 h, range 0.0–55.1 h). Peak interstitial glucose levels occurred predominantly, but not exclusively, in the afternoon (13.00–15.00) and evening (19.00–22.00); however, elevated levels were noted throughout the 24-h period. Baseline HbA_{1c} was independently associated with severity and duration of elevated glucose levels in a regression adjusted for baseline BMI.

Conclusions These data report for the first time that high glucose levels are encountered by nearly all women following this regimen, the severity and duration of which are independently associated with HbA_{1c}. Further work is required to determine if controlling glucose levels during treatment influences outcome.

<H1>Introduction

Glucocorticoids are anti-inflammatory and immunomodulatory medications widely employed in the treatment of inflammatory and neoplastic conditions [1]. In the context of taxane- and platinum salt-based chemotherapy, dexamethasone is effective in reducing hypersensitivity reactions and delayed toxicity, particularly emesis, and as such is widely incorporated into chemotherapeutic regimens [2].

However, hyperglycaemia is a common and unwanted side-effect of supraphysiological, acute glucocorticoid therapy. Mechanistically, this is driven by impaired insulin action and peripheral glucose uptake in addition to suppression of pancreatic β-cell function [3,4]. Both Type 1 and Type 2 diabetes mellitus are associated with negative health outcomes in cancer treatment, including an increased incidence of bacteraemia, a higher incidence of drug toxicity and increased all-cause mortality [5–7]. Specifically, in gynaecological cancer, impaired fasting glucose was associated with a significant reduction in disease-free survival even at a modest threshold of 5.5 mmol/l [8–10]. The reason for this observation is unclear and may not be due to hyperglycaemia *per se*. Possible explanations include the association of diabetes with micro- and macrovascular disease or the presence of hyperinsulinemia. However, pre-clinical *in vitro* studies suggest that hyperglycaemia attenuates the efficacy of chemotherapeutic agents on the majority of cancer cell lines, including ovarian tumour cells, by a variety of mechanisms including modification of apoptotic and cell proliferation signalling [11]. In human samples, upregulation of the GLUT1 transmembrane glucose transporter is an indicator of ovarian neoplastic transformation and an independent predictor of poor prognostic outcome [12,13]. Together, these studies suggest that hyperglycaemia may have an independent effect on treatment outcome although human data supporting this are lacking.

Despite these observations, the true diurnal glucose profile of people treated with high-dose dexamethasone as part of an outpatient chemotherapy regimen is unknown because previous studies have typically utilized finger-prick capillary glucose testing four to six times daily, generating a limited picture of blood glucose variability throughout an extended treatment period. To address this, we performed blinded continuous interstitial glucose monitoring (CGM) on a cohort of 16 women undergoing carboplatin/paclitaxel chemotherapy combined with high-dose dexamethasone treatment for gynaecological cancer in the outpatient setting. CGM measures the glucose concentration of interstitial subcutaneous fluid continuously via a device adherent to the skin

surface. In this way, CGM allows estimation of serum glucose levels over long periods and in this context such information may significantly inform the development of current guidelines on the screening and management of steroid-induced hyperglycaemia [14,15].

<H1>Participants and methods

Sixteen women with confirmed gynaecological cancer were recruited into the study at the point of referral for combined carboplatin and paclitaxel outpatient chemotherapy treatment (carboplatin AUC = 6 mg/h/l, paclitaxel 175 mg/m^2) between 2013 and 2015. Women with a WHO performance status > 2 or recent (1 month) history of glucocorticoid use were excluded. Baseline anthropomorphic variables and family history were recorded, and blood drawn for measurement of HbA_{1c}. The day before chemotherapy/dexamethasone treatment (day 0), women were fitted with a Medtronic iPRO2™ CGM device (Medtronic, Northridge, CA, USA). On the day of chemotherapy (day 1), women were treated with high-dose dexamethasone (20 mg at 04.00 and 10 mg at 10.00) followed by 4 mg twice daily (08.00 and 12.00) for three subsequent days (days 2–4). Blinded interstitial glucose measurements were recorded at 5-min intervals from day 0 to day 5 inclusive and were analysed at the end of the study period. The time course of treatment and glucose observations is depicted in Fig. 1. An interstitial glucose level of 11.1 mmol/l was chosen as a ceiling threshold in this study because it is a level women without diabetes would be unlikely to display on a standard day. The study was approved by the National Health Service (NHS) Lothian research ethics committee and all women gave written informed consent. CGM devices were calibrated four times daily using finger-prick capillary blood glucose readings.

<H2>Participant characteristics

Of sixteen women, one discontinued CGM after 3 days (completing days 0, 1 and 2) and these data are included in the final analysis. A total of 93 CGM days were analysed, totalling 23 653 individual interstitial glucose readings. Baseline characteristics of the women in the study included are in Table 1. Mean age was 60.1 years (SD ± 8.8) with a mean BMI of 29.1 kg/m^2 (SD ± 5.4). All but one woman had a diagnosis of ovarian cancer; the remaining woman had endometrial cancer. None had a diagnosis of diabetes mellitus or a history of gestational diabetes mellitus. Baseline HbA_{1c} concentration was beneath the WHO diagnostic criterion for diabetes (HbA_{1c} ≥ 48 mmol/mol; 6.5%) in all women; one had an HbA_{1c} of 44 mmol/mol (6.2%), which met WHO diagnostic criterion for pre-diabetes (HbA_{1c} 42–47 mmol/mol, 6.1–6.5%).

<H2>Statistical analysis

Raw data were uploaded and processed in R version 3.2.2 (https://www.r-project.org/). Meaningful visualization of the CGM data and comparison between women was challenging due to marked variation in mealtimes and activity levels with subsequent temporal variation in interstitial glucose excursions. Heat mapping is a method of visualizing data, whereby individual values are represented as points on a colour spectrum. This method was employed to depict the diurnal variation in interstitial glucose levels throughout the study period using the heatmap.2 function in gplots for R (www.cran.r-project.org/web/packages/gplots). To identify independent associates of severity and duration of glucose excursions on each day of CGM analysis, lme4 package (https://cran.r-project.org/web/packages/lme4/index.html) in R was used to create mixed-effects linear models. The outcomes 'peak daily interstitial glucose' and 'duration of raised interstitial glucose' were each individually modelled against HbA_{1c} and BMI with the inclusion of individual women and treatment day as crossed random effects to account for repeated testing of each woman and the standardized

dexamethasone regime. Other graphical outputs were generated using ggplot2 package (www.ggplot2.org/).

<H1>Results

<H2>Interstitial glucose

Raised interstitial glucose was virtually ubiquitous among women receiving dexamethasone in combination with carboplatin and paclitaxel chemotherapy. Some 15 of 16 (94%) women exhibited raised interstitial glucose (> 11.1 mmol/l) on day 1 of the treatment protocol, following the highest dose of dexamethasone (30 mg total dose). On day 5, 24 h following the cessation of dexamethasone, only 2 of 15 women (13%) continued to demonstrate elevated interstitial glucose (Fig. 2). Peak interstitial glucose levels were highest on day 1 of treatment with a median peak glucose achieved of 14.5 mmol/l (range 10.2–22.2 mmol/l). On day 5, median peak interstitial glucose was 8.8 mmol/l (range 6.7–17.5) mmol/l.

The burden of raised interstitial glucose, as determined by time spent ≥ 11.1 mmol/l, also varied considerably (Fig. 3). Time spent in the raised glucose range was greatest on day 1 of treatment (median 2.75 h, range 0.00–9.95 h) and lowest on day 5 (median 0.0 h, range 0.00–7.95 h). Total time spent within the raised glucose range over the CGM monitoring period following the initiation of glucocorticoid therapy was equally variable (median 3.6 h, range 0.0–55.1 h).

<H2>Characterization of the interstitial glucose diurnal rhythm

Visualization by heat map demonstrated that raised interstitial glucose was typically greatest in the afternoon with fasting glucose levels comparatively unaffected (Fig. 4). However, elevated glucose

levels of > 11.1 mmol/l were noted in the majority of women throughout the night on each treatment day until the morning of day 5, and daily peak glucose levels for many women in the study occurred after midnight (00.00– 03.00) on days 2, 3 and 4 of the monitoring period. This suggests that dysglycaemia as a consequence of twice-daily dexamethasone treatment (08.00 and 12.00) continues over the 24-h period.

<H2>Effect of baseline HbA_{1c}

Baseline HbA_{1c} was independently associated with peak level of interstitial glucose and the duration of raised interstitial glucose. The linear mixed model regression analysis took into account the fact that glucose levels were measured in each woman on five separate days of the same steroid treatment protocol. This revealed that baseline HbA_{1c} was independently associated with both severity of hyperglycaemia, as measured by peak glucose level (slope coefficient = 0.53, P = 0.01), and duration of glucose excursions (slope coefficient = 0.43, P = 0.03) in a regression adjusted for BMI. As, such the estimated increase in peak glucose level was 0.53 mmol/l and duration of glucose excursions was 0.43 h for each mmol/mol increase in HbA_{1c} (Table S1).

One woman in the study had an HbA_{1c} in the pre-diabetes range (44 mmol/mol; 6.2%). She was noted to have a considerably greater severity and duration of raised interstitial glucose on each day of the study, spending 55 h with an interstitial glucose > 11.1 mmol/l with a level > 20 mmol/l on each day of steroid administration (Fig. 4, participant 10*).

<H1>Discussion

These data examine in detail for the first time the diurnal character of interstitial glucose levels in an unselected group of women receiving dexamethasone in the context of paclitaxel/carboplatin chemotherapy for gynaecological cancer. Interestingly, we found that raised interstitial glucose was present at some point in almost all women (94%) in this cohort. This is in contrast to previous reports of glucocorticoid use, which reported an incidence of 9.4 to 50% depending on the population studied, glucocorticoid dose and duration, and clinical context [16–24]. One study of acute glucocorticoid use in a hospitalized population reported that > 50% of those receiving high-dose glucocorticoids (≥ 40 mg prednisolone equivalents) exhibited at least one episode of hyperglycaemia [24]. Reasons for the comparatively high level of hyperglycaemia noted in this cohort are: (1) the use of CGM rather than pre- or post-meal blood glucose testing is likely to capture otherwise unobserved glucose excursions; (2) the glucocorticoid dose in our cohort was considerably higher than in previous studies (30 mg dexamethasone on day 1, 200 mg prednisolone equivalents vs. 40 mg prednisolone equivalents [24], given twice daily rather than as a once-daily morning dose); (3) women in our study had the combined effect of glucocorticoid exposure and the physiological stress of chemotherapeutic agents; and (4) this study measured interstitial glucose levels, whereas previous reports have typically examined whole blood glucose measurement. Given the possibility that hyperglycaemia may influence disease-free survival, this is an important observation.

As with previous studies, we found that peak glucose levels were detected in the late afternoon in most cases [25]. We also demonstrated, however, that high glucose levels do occur throughout the night and that significant peaks in glucose could arise up to 03.00, before declining to fasting levels. This is likely due the combined effects of using glucocorticoids in the early part of the day to avoid insomnia and the effect of glucocorticoids on insulin uptake and postprandial hyperglycaemia. We

would advocate on the basis of this study that capillary blood glucose levels measured between 15.00 and 17.00 and between 19.00 and 22.00 are most likely capture peak glucose and thus optimally estimate the severity of hyperglycaemia in this chemotherapy/dexamethasone regime. Our data also suggest that individuals on twice-daily dexamethasone may require long-acting basal insulin or twice-daily fixed mix insulin to maintain adequate glucose control as recommended in current guidance [14]. Further studies are required to compare these findings with diurnal glucose profiles in other chemotherapy treatments with different dexamethasone doses and intervals. Although CGM is not routinely used for glucose monitoring in this context, the advent of 'flash' glucose monitoring systems makes this an entirely feasible prospect for future cancer care.

Interestingly, in this study, we identified that HbA_{1c} level, although normal in all but one woman, was associated with both severity and duration of raised interstitial glucose. This is in contrast to other published works which have consistently indicated that BMI and age were the dominant predictors of dysglycaemia, as well as dose and duration of glucocorticoid therapy [17]. We speculate that this finding is due the immediate measurement of glucose levels after comparatively high-dose glucocorticoid rather than following protracted treatment of moderate dose glucocorticoid therapy, as observed previously [17]. HbA_{1c} may be a more accurate reflection of insulin sensitivity and pancreatic β-cell function, which are immediately challenged by high-dose glucocorticoid exposure, whereas elevated BMI and increasing age may confer susceptibility to the obesogenic and dyslipidaemic effects of chronic supraphysiological glucocorticoid exposure.

One woman in this study had pre-diabetes with an HbA_{1c} of 44 mmol/mol (6.2%). This woman exhibited more severe and protracted raised interstitial glucose, with a peak glucose of 22.2 mmol/l; interstitial glucose levels were raised for over 55 h and remained elevated 24 h following cessation

of dexamethasone. Although this is a single case, it suggests that an HbA_{1c} in the pre-diabetes range confers high risk of a significant prolonged hyperglycaemic state in people on this regimen.

Further work is now warranted to determine whether maintenance of euglycaemia affects outcome in individuals with hyperglycaemia induced by chemotherapeutic regimes. It is important to note that what we have defined as raised interstitial glucose in this study (11.1 mmol/l) was chosen as it is a level women without diabetes would be unlikely to display without some level of physiological stress or pharmacological intervention. If indeed hyperglycaemia does independently effect outcome, the physiological level and duration at which this occur are unknown. Importantly, *in vitro* studies in which hyperglycaemia was detrimental to anti-mitotic treatment were conducted at significantly higher levels (25 mmol/l) [11].

To our knowledge, only one randomized control study of intensive glycaemic control during chemotherapy has been reported. Vu and colleagues examined the effect of intensive insulin therapy using a basal bolus regime, dietary advice and education vs. standard care in unselected individuals treated for haematological malignancy. Despite improved control, there was no improvement in outcome and secondary analysis suggested that high levels of exogenous insulin may be associated with early relapse [26]. By contrast, the insulin sensitizer metformin has been associated repeatedly with a reduced risk of multiple cancer types [27,28] and early prospective studies in ovarian cancer treatment are encouraging [29]. As such, there is clear need for a large prospective randomized trial on the routine use of other agents that prevent hyperinsulinemia as an adjunct to carboplatin/paclitaxel/dexamethasone chemotherapy and indeed many such trials are currently registered and actively recruiting.

In conclusion, raised interstitial glucose is present in almost all women undergoing this treatment regimen, and typically peaks within the 13.00–17.00 and 19.00–20.00 periods. Baseline HbA_{1c} is associated with the severity and duration of glucose excursions. Further studies are awaited to determine the effect of oral hypoglycaemic agents on outcome.

Funding sources

Competing interests

None declared.

Acknowledgements

Medtronic iPRO2™ devices were supplied by Medtronic (Northridge, CA, USA). Clinical assessments were performed at the Wellcome Trust Clinical Research Centre, Western General Hospital, Edinburgh, UK.

References

1 Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. Rheumatology 2011; **50**: 1982–1990.

2 Boulanger J, Boursiquot JN, Cournoyer G, Lemieux J, Masse MS, Almanric K *et al*. Management of hypersensitivity to platinum- and taxane-based chemotherapy: cepo review and clinical recommendations. *Curr Oncol* 2014; **21**: e630–e641.

3 Van Raalte DH, Nofrate V, Bunck MC, Van Iersel T, Schaap JE, Nässander UK *et al*. Acute and 2-week exposure to prednisolone impair different aspects of β-cell function in healthy men. *Eur J Endocrinol* 2010; **162**: 729–735.

4 Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism. *Endocrinol Metab Clin North Am* 2014; **43**: 75–102.

5 Jung S-H, Jang H-C, Lee S-S, Ahn J-S, Yang D-H, Kim Y-K *et al*. The impact of hyperglycemia on risk of severe infections during early period of induction therapy in patients with newly diagnosed multiple myeloma. *Biomed Res Int* 2014; **2014**: 413149.

6 Wu W, Merriman K, Nabaah A, Seval N, Seval D, Lin H *et al*. The association of diabetes and anti-diabetic medications with clinical outcomes in multiple myeloma. *Br J Cancer* 2014; **111**: 628–636.

7 Derr RL, Hsiao VC, Saudek CD. Antecedent hyperglycemia is associated with an increased risk of neutropenic infections during bone marrow transplantation. *Diabetes Care* 2008; **31**: 1972–1977.

8 Lee YY, Choi CH, Kim CJ, Song TJ, Kim MK, Kim TJ *et al*. Glucose as a prognostic factor in non-diabetic women with locally advanced cervical cancer (IIB-IVA). *Gynecol Oncol* 2010; **116**: 459–463.

9 Lamkin DM, Spitz DR, Shahzad MMK, Zimmerman B, Lenihan DJ, Degeest K *et al*. Glucose as a prognostic factor in ovarian carcinoma. *Cancer* 2009; **115**: 1021–1027.

10 Li J, Wu M, Lu H, Zhang B, Wang L, Lin Z. Impact of hyperglycemia on outcomes among patients receiving neoadjuvant chemotherapy for bulky early stage cervical cancer. *PLoS One* 2016; **11**: e0166612.

11 Gerards MC, van der Velden DL, Baars JW, Brandjes DPM, Hoekstra JBL, Vriesendorp TM *et al*. Impact of hyperglycemia on the efficacy of chemotherapy – a systematic review of preclinical studies. *Crit Rev Oncol Hematol* 2017; **113**: 235–241.

12 Rudlowski C, Moser M, Becker AJ, Rath W, Buttner R, Schroder W *et al*. GLUT1 mRNA and protein expression in ovarian borderline tumors and cancer. *Oncology* 2004; **66**: 404–410.

13 Cantuaria G, Fagotti A, Ferrandina G, Magalhaes A, Nadji M, Angioli R *et al*. GLUT-1 expression in ovarian carcinoma: association with survival and response to chemotherapy. *Cancer* 2001; **92**: 1144–1150.

14 Roberts A, James J, Dhatariya K; Joint Diabetes Societies for Inpatient Care. *Management of Hypoglycaemia and Steroid (Glucocorticoid) Therapy*, October 2014. Available at http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_Steroids.pdf Last accessed XX XXX XXXX.

15 Peoples T, Bailey T, Ronald B, Zisser HC, Janowski B, Huang S *et al*. Accuracy performance of the Medtronic NexSensor for 6 days in an inpatient setting using abdomen and buttocks insertion sites. *J Diabetes Sci Technol* 2011; **5**: 358–364.

16 Gonzalez-Gonzalez JG, Mireles-Zavala LG, Rodriguez-Gutierrez R, Gomez-Almaguer D, Lavalle-Gonzalez FJ, Tamez-Perez HE *et al*. Hyperglycemia related to high-dose glucocorticoid use in noncritically ill patients. *Diabetol Metab Syndr* 2013; **5**: 18.

17 Clore J, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. *Endocr Pract* 2009; **15**: 469–474.

18 Uzu T, Harada T, Sakaguchi M, Kamasaki M, Isshiki K, Araki S *et al*. Glucocorticoid-induced diabetes mellitus: prevalence and risk factors in primary renal diseases. *Nephron Clin Pract* 2007; **105**: 15–18.

19 Yan X, Wong P, DelPriore G, Bottino J. Chemotherapy-associated steroid use and its effect on blood glucose, nephro-, and other toxicity of chemotherapy for non-diabetic oncological patients. *J Clin Oncol* 2009; **27**: e20721.

20 Liu X, Zhu X, Miao Q, Ye H, Zhang Z, Li Y-M. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. *Ann Nutr Metab* 2014; **65**: 324–332.

21 Ha Y, Lee K-H, Jung S, Lee S-W, Lee S-K, Park Y-B. Glucocorticoid-induced diabetes mellitus in patients with systemic lupus erythematosus treated with high-dose glucocorticoid therapy. *Lupus* 2011; **20**: 1027–1034.

22 Angelopoulos TP, Tentolouris NK, Bertsias GK, Boumpas DT. Steroid-induced diabetes in rheumatologic patients. *Clin Exp Rheumatol* 2014; **32**: 126–130.

23 Petersons CJ, Mangelsdorf BL, Jenkins AB, Poljak A, Smith MD, Greenfield JR *et al*. Effects of low-dose prednisolone on hepatic and peripheral insulin sensitivity, insulin secretion, and abdominal adiposity in patients with inflammatory rheumatologic disease. *Diabetes Care* 2013; **36**: 2822–2829.

24 Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. *Endocr Pract* 2006; **12**: 358–362.

25 Burt MG, Roberts GW, Aguilar-Loza NR, Frith P, Stranks SN. Continuous monitoring of circadian glycemic patterns in patients receiving prednisolone for COPD. *J Clin Endocrinol Metab* 2011; **96**: 1789–1796.

26 Vu K, Busaidy N, Cabanillas ME, Konopleva M Faderi S Thomas DA *et al*. A randomized controlled trial of an intensive insulin regimen in patients with hyperglycemic acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk* 2012; **12**: 355–362.

27 Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. *PLoS One* 2012; **7**: e33411.

28 Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B *et al*. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer Prev Res (Phila)* 2010; **3**: 1451–1461.

29 Dilokthornsakul P, Chaiyakunapruk N, Termrungruanglert W, Pratoomsoot C, Saokaew S, Sruamsiri R. The effects of metformin on ovarian cancer: a systematic review. *Int J Gynecol Cancer* 2013; **23**: 1544–1551.

FIGURE 1 Schematic of study design. On day 1, 20 mg of dexamethasone was given at 04.00 with a further 10 mg at 10.00. On days 2–4, 4 mg dexamethasone was administered at 08.00 and 12.00.

FIGURE 2 Boxplot with overlying jitter plot of peak glucose level observed in each participant on each study day. Dashed line indicates 11.1 mmol/l threshold. Each point represents one person.

FIGURE 3 Boxplot with overlying jitter plot of time spent with a raised interstitial glucose (> 11.1 mmol/l) for each participant on each day of the study. Each point represents one person.

FIGURE 4 Heat map visualization of glucose levels for all participants through the course of the study. Each row depicts glucose levels for one person. The participant with an HbA_{1c} in the 'pre-diabetes' range (44 mmol/mol, 6.2%) is identified by * on each day. Glucose levels: blue, < 11.1 mmol/mol; white, 11.1 mmol/mol; red, > 11.1 mmol/mol.

<H1>Supporting Information

Additional Supporting Information is available in the online version of this article:

Table S1 Output of linear mixed model repeated measures analysis.

Table 1 Baseline characteristics of women included in the study analysis

ID	Age (years)	HbA_{1c} [mmol/mol; (%)]	BMI	History of diabetes	Family history of diabetes	Cancer diagnosis
1	52.3	34 (5.2)	26.3	No	No	Stage III Grade 3 ovarian cancer
3	69.2	35 (5.3)	32.1	No	No	Stage III C grade 3 serous papillary ovary cancer
4	60.1	40 (5.8)	23.7	No	Yes; nephew Type 1 diabetes	Relapsed serous papillary ovarian cancer
5	65.2	35 (5.3)	34.3	No	Yes; sister Type 2 diabetes, niece Type 1 diabetes	Stage 1A clear cell ovarian carcinoma
6	64.7	38 (5.6)	27.3	No	No	Stage III C serous papillary carcinoma
7	74.2	38 (5.8)	25.1	No	No	Stage III C ovary cancer
8	57.0	40 (5.8)	38	No	No	Relapsed ovarian cancer Stage IV
9	70.0	39 (5.7)	28	No	No	Stage III C Grade 3 Serous papillary adenocarcinoma
10	70.0	44 (6.2)	30.4	No	No	Relapsed ovarian cancer
11	66.0	33 (5.2)	21.7	No	No	Clear cell adenocarcinoma
12	46.7	35 (5.3)	40	No	Yes; mother and father Type 2 diabetes	Stage 1 A High grade endometroid ovarian cancer
13	61.0	38 (5.6)	24.4	No	Yes; grandmother Type 2 diabetes	Stage III C High grade serous ovarian cancer
14	55.8	41 (5.9)	34.2	No	No	Stage III C High grade serous ovarian cancer
17*	55.4	33 (5.2)	24.8	No	No	Stage III C High grade serous ovarian cancer
18	42.9	31 (5.0)	22.2	No	No	Stage 2 B Grade 2 endometroid adenocarcinoma
19	50.7	39 (5.7)	32.3	No	No	Stage II C clear cell of the ovaries
Mean	60.1	37.1	29.1			
SD	8.8	3.4	5.4			

*Participant 17 discontinued continuous glucose monitoring after day 1.

Figure 1

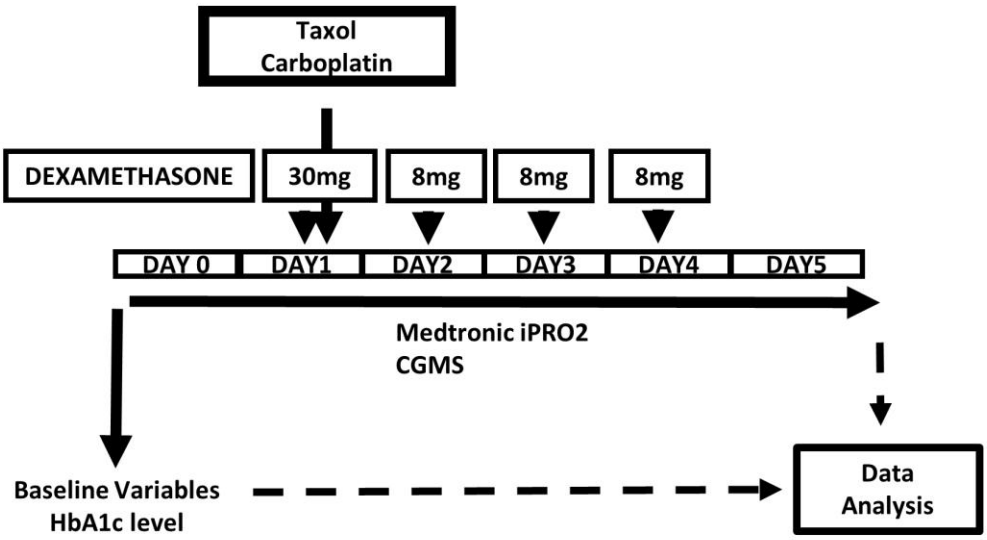

Figure 2

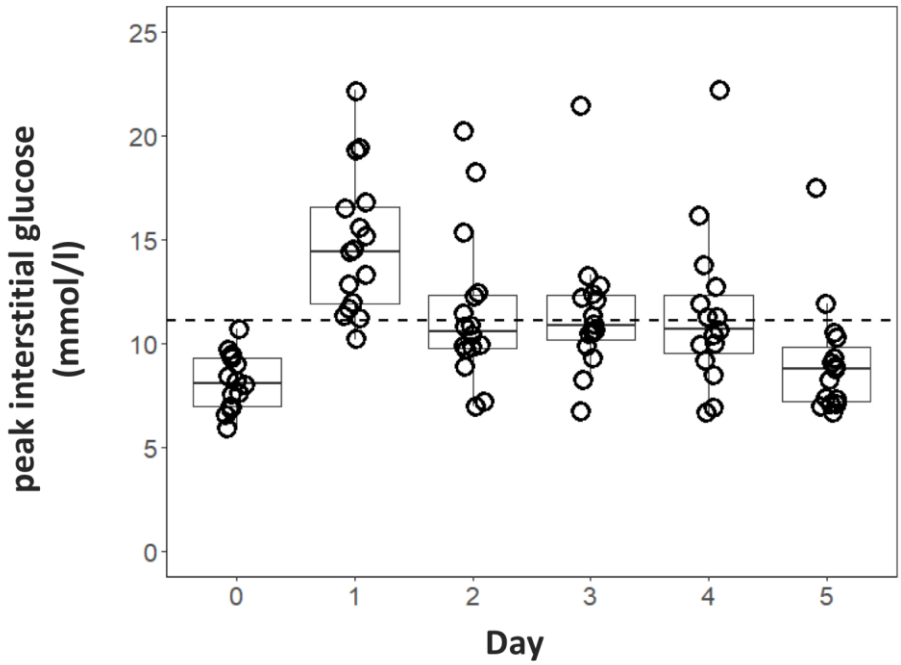

Figure 3

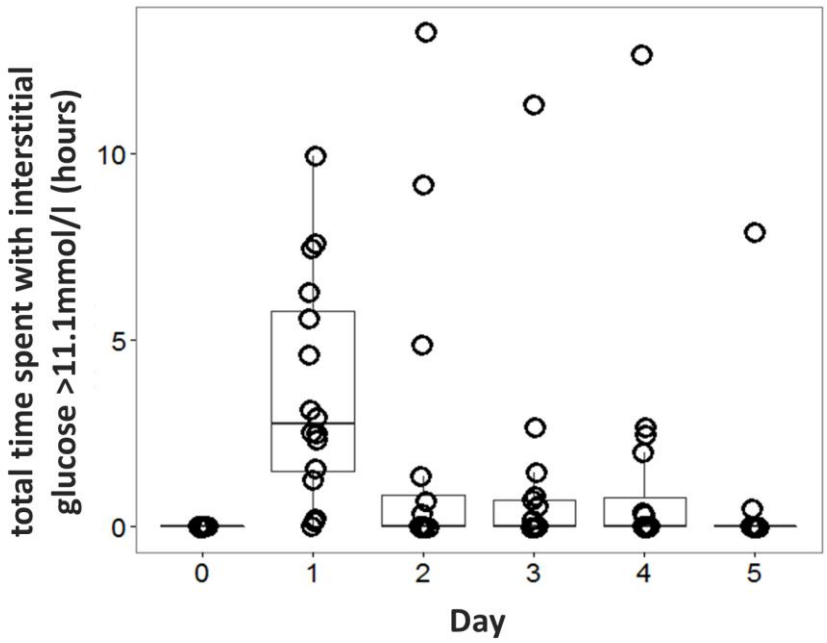

Figure 4